

Trip Report by S. C. Finch to  
Kiev, Ukraine 9/21-23, 1998

The initial meeting was held on 9/21/98 in Dr. Romanenko's office. Present were Drs. Romanenko, Bebeshko, Dyagil, Klimenko, Pyatak, Bazyka, Tsvetkova, Burch and Finch. Following the usual greetings by Dr. Romanenko he indicated that he very much favored small meetings such as we were having but he would like to get the agenda well in advance. I advised him that the agenda was sent a week previously but we would try to send it more in advance in the future. Dr. Romanenko then requested an agenda for our meeting. I told him that we had 3 objectives but the most important was the first which was described as our hope to finalize the hematology review process. We also hoped to review progress in hematology as outlined in the 3<sup>rd</sup> Quarter report with emphasis on the follow-up of the liquidators who were identified in Dnepropetrovsk for dosimetry questionnaires and processing of blood samples. I indicated that my 3<sup>rd</sup> objective was to meet with Dr. Pilinskaya with regard to the problems which she continues to have with implementing FISH studies in her laboratory.

We were transported to the new Clinical Radiation Center for Chernobyl and commenced our next meeting at about 11:00 am. Present were Drs. Dyagil, Gudzenko, Klimenko, Tsvetkova, Burch and Finch. It was mentioned that the hospital would be dedicated with WHO in December. It is partially complete now but is functioning as a laboratory, hospital and polyclinic. It was noted that Puscha Voditsa will become a rehab and recreation center for the clean-up workers. The next 2 hours were spent with detailed review of the draft plan for the hematology review program. Previous draft had indicated that the age of the liquidators to be studied was 40-60 in 1986. This was changed to ages 20-40. A decision was made to have all of the available hematology slides sent for review rather than just the best slides. It was decided that the best place to stain or restain blood smears is the laboratory in Kiev but if sections were to be made from paraffin blocks they would have to be cut in the oblast hospital laboratories. It was recommended that the hospital's be reimbursed \$5.00 for each paraffin block which is cut. There was considerable discussion as to who should abstract the case histories. Dr. Dyagil and Klimenko felt that this should not be done by local hospital personnel if one is to achieve an acceptable level of uniformity. They strongly recommended that 2 of the hematologists from their laboratory go to each location and abstract the clinical records. It was recommended that Dr. Klimenko rather than either Dr. Bebeshko or Dr. Romanenko contact the appropriate staff members at each of the oblast hospitals regarding the plan for abstracting records and collecting slides. It was agreed that at each location an additional case of multiple myeloma and 2 cases of either myelofibrosis or hypoplastic anemia should be added. It was pointed out by the Ukrainian hematologists that some of the early cases of myelodysplasia may have been diagnosed as myelofibrosis or hypoplastic anemia and the only way in which we would probably be able to make sure of this would be to ask for early and late cases of each type. The remainder of the morning was spent considering the method of randomized selection of cases. It eventually was decided that we would try to focus on 3 time periods (87-90, 91-94, and 95-98). If 2 cases of a disorder were requested we would request 1 in the early period and 1 in the late period. If 3 cases were requested there would be 1 in each period

and if 5 cases were requested there would be 2 in the early period, 1 in the middle period and 2 in the late period. This would give us from each location a total of 20 cases with 9 in the early period, 2 in the middle period and 9 in the late period. The maximum number of cases to be reviewed from all locations would be 120. The actual number might be closer to 100 as some cases will have no slides and it is unlikely that many cases of myelodysplasia will be identified during the early period. The actual method of randomized selection of cases within each time period was left to Drs. Gudzenko and Burch.

The meeting regarding the hematology review process continued with the same personnel from about 1:30 to 3:00 p.m. on the 21<sup>st</sup> of September. Most of that time was devoted to making initial plans for the actual conduct of the meeting in Kiev. It was decided that probably we should plan to review the leukemias, myeloma and related disorders first followed by the lymphomas. It may be that some of the hematologists may elect to not become involved with any, or all of the lymphomas so that it would be best not to mix the cases. The evaluation sheets for leukemia and related disorders will be quite different from those for lymphoma. It was emphasized that the evaluation sheets need not be signed. We are interested in comparisons of diagnostic impressions by each member of the panel but we would not like to make that one of the stated objectives of the review process. There are ways of making comparisons without requiring signatures. In view of the experience with the Consortium group in their hematology review we felt that it might be best to have cases reviewed in groups of 5 with 1 case located at each of 5 microscopes in such a way that the hematologists can rotate from 1 scope to another in order to make their reviews. Each of the 5 cases then can be reviewed before moving on to the next 5. In advance of the meeting Dr. Dyagil and her associates will identify the best slides to be placed on the microscopes in order to facilitate the review process. There was a considerable amount of discussion regarding the labeling and identification of slides. The final decision was that the original label on the slide would not be changed as it would be extremely difficult to do this without damaging the original labels or without the risk of removing them completely. It was decided that in advance of the meeting the slides for a particular individual would be placed in a single folder and that the folders would be labeled consecutively. A record of each case will be kept on a master sheet so that we will know from where it originated. It should be much easier for the reviewers to identify each case by the consecutive numbers given to them in Kiev than by the name of the individual or the code number which might be on the slide. Another decision that was made was not to necessarily try to conceal the clinical diagnosis. None of the diagnoses will have FAB type and it is unlikely that clinical impressions will influence an expert group of hematologists who will base their opinions to some extent on interpretations of the abstracted clinical information but mostly on their own interpretations of the morphology they observe under the microscope. Other considerations at the meeting were the importance of having good lighting, good microscopes, an overhead projector, a slide projector and good translation. Dr. Gudzenko indicated that she would plan to initiate her visits to the various oblasts during the 2<sup>nd</sup> and 3<sup>rd</sup> weeks of October and that her work should be done by November 10<sup>th</sup>. She was to be followed by the hematologists who would abstract cases and identify slides. It was agreed that all of the abstracted case information and slides should be in Kiev by

December 10<sup>th</sup> and that the best times for the hematology review would be either the 2<sup>nd</sup> or 3<sup>rd</sup> week in January of 1999. It was recommended by our Ukrainian colleagues that the results of the cases reviewed be transmitted to the hematologists in the various oblasts for their information upon completion of the review process..

The group reconvened the morning of Tuesday (9/22/98) for consideration of costs and other practical aspects of the review. It was recommended that each of the Ukrainian expert reviewers should receive about \$50.00 per day as they would be on unpaid leave. Dr. Gudzenko and each of the hematologists each would plan to take 2 trips in order to complete their work at each of the locations of interest. Dr. Gudzenko would be away for approximately 6 days and each of the hematologists would be away about 4 days. It was estimated that food and local transportation expenses for each person would be about \$20.00 a day and lodging would be about \$30.00 per day total transportation costs would be estimated at about \$420.00. Although the slides collected from each location would be hand carried to Kiev they would be returned by mail at an estimated cost of about \$60.00. Other expenses would be those for coffee breaks, slide folders, renting a slide projector, illustration pad, pens and paper. Other considerations for the meeting would be supplemental heat, having a copier available in the building and access to telephone. A possible expense might be that of paying the local hospital offices for any expenses involved in pulling records and slides. I suggested that some reimbursement might be reasonable if this was done during other than the regular working hours but I did not think that this should necessarily be a reimbursable cost.

Tuesday afternoon - 1:30 to 3:00 p.m. I reviewed with Drs. Dyagil and Klimenko the hematology sections of the 3<sup>rd</sup> quarter milestone report. In milestone #20 I asked for their criteria for leukemia case classifications of definite, probable or possible. They indicated that these categorizations were based only on conclusions from evaluation of the clinical records. For milestone #22 it was emphasized that the proposed plan for the hematology review is to abstract clinical records rather than to request the complete medical record. I also emphasized that the method of case randomization remains to be determined. It was noted in milestone #23 that the search for new cases of leukemia now has been completed from only 1987 to 1990. Most unusual were the 22 cases of polycythemia vera and 48 cases of multiple myeloma diagnosed in 1990, a relatively large number in comparison to previous 2 years. Also it was pointed out that some cases of subleukemic myeloid leukemia may represent cases of myelodysplasia or preleukemic disorders. It was mentioned in milestone #26 that red cells from the high-dose liquidators were frozen but not in accord with the method of Jensen for storage with the ultimate aim of doing red cell GPH determinations. I pointed out to them that red cells directly frozen would hemolyze upon thawing and would not be suitable for GPH studies. Also the red cells were not checked for their M & N antigens. I was told that the reasons for not completing these tasks was due to their not having received M & N antisera and the reagents for freezing red cells by the Jensen method. I told them I would check on the status of these reagents upon my return. Furthermore, they indicated that they do not have a copy of the Jensen red cell freezing method which I sent to Dr. Bebeshko one or two years ago. Again I told them that I would send another copy upon my return home.

In milestone #27 it was mentioned that a sample of lymph node was stored in formalin. I urged them also to freeze and retain some fresh tissue in the future.

In milestone #29 mention is made of "The Republican Specialized Dispensary". I made inquiry regarding this dispensary and was told that it was a specialized dispensary for liquidators. Presumably this dispensary is being contacted in order to try to identify more high-dose liquidators.

The group was complemented for developing an operations manual regarding management of members of the subcohort. They feel that this will be very useful.

From 3-5 p.m. that same afternoon I visited Dr. Maria Pilinskaya in her laboratory. Also present was Sergey Dybski. The laboratory appeared to be well equipped with 2 excellent fluorescent microscopes and several other good microscopes. Dr. Pilinskaya was pleased that she had just received a new freezer but she continued to lament the fact that she still needs many reagents and 3 items which are essential for her doing FISH determinations. These are a lamp, a filter and the DNA probes. She also was under the impression that culture media and other reagents which she had ordered may have been diverted to Dr. Bebeshko's laboratory. I reassured her that I would check on the progress of her orders and possible diversions of her laboratory supplies to Dr. Bebeshko's laboratory. I had an opportunity to examine several metaphase spreads under the microscope. They were of excellent technical quality. I told Dr. Pilinskaya that I had talked to Dr. Niel Wald at The University of Pittsburgh and that he was pleased to be able to accommodate Sergey Dybsky for a period of training in the field of leukemia cytogenetics. Dr. Pilinskaya told me that the plan was to have him stay there for 4-6 weeks. She did not know how he was to be funded during that period of time. Dr. Pilinskaya also stressed her lack of scientific communication with the outside world. She receives no foreign medical journals but does receive the RERF bulletin. She and Sergey Dybsky were anxious to join a cytogenetic society in France but have been unable to transfer currency for the registration. I offered to register for them but she rejected the offer as registration would be much more expensive from the US than from Ukraine. I suggested to her that she might be able to arrange this through Dr. Tirmarche when she visits in Kiev the week after my visit. She agreed to this arrangement.

On Wednesday morning (9/23/98) we met with Dr. Tsvetkova, Dr. Dyagil, Dr. Klimenko, Dr. Gudzenko and Dr. Pilinsyaka.. Dr. Tsvetkova informed us that she had been unable to locate pathology slide folders in Kiev that are suitable for our hematology review program. We agreed that we would try to locate these in the States and that Dr. Burch would hand carry some during his next visit. Discussion then turned to the experience with interviewing 20 liquidators in the field for task #30. The experience with these 20 persons was outlined in the third quarter report. Concern was expressed regarding the relatively poor liquidator response to the preliminary invitations by one of the doctors. The plan is to invite the next 20 by letter and to try to arrange for closer contacts with the doctors in the program. It was noted that the motivation for liquidators to participate is not strong and the opinion was expressed that they need some compensation. It was suggested that this be in the range of about \$10.00 for each visit

which was the amount used for the WHO leukemia study. The other problem concerned the amount of blood that is to be removed for special studies. No blood samples were taken from the liquidators who did respond. It finally was agreed that 20ml rather than 40ml of blood would be adequate to complete the required biodosimetry and hematology laboratory studies. The proposal is that 2 10ml vacutainers of venous blood be drawn and sent to Kiev for distribution. From Dnepropetrovsk it was felt that the blood could arrive in Kiev well within the critical 24 hour period so that pre-shipment separation of the mononuclear cells at the oblast level would not be necessary. One of the current problems that they are having is that they do not have the proper containers in which they can ship the blood. I assured them that these have been ordered and would be forthcoming. The plan is that when the tubes of blood arrive in Kiev that one of the tubes will go to Dr. Pilinskaya's laboratory for FISH determinations and the other tube will go to hematology for cryopreservation of the mononuclear cells and plasma. Blood samples from the high-dose group would be managed in the same way except that they would be phenotyped for M & N blood groups for the purpose of red cell cryopreservation if they are heterozygotic. It was also pointed out during this discussion that blood could not be taken from these persons unless they read and sign the consent form. I also mentioned that we could not make any decision regarding compensation for the liquidators until it had been approved by Dr. Masnyk, Dr. Romanenko and others who control funding and policy making decisions.

Dr. Tsvetkova then briefly reviewed the experience that she and others had had visiting several of the oblasts scheduled for participation in Phase I of the program. The first trip was to Sumskaya oblast with Drs. Dyagil and Klimenko during 6-8 of August. They obtained the approval of the Chief of the Oblast Medical Services to have the various hospitals work with the project. The second trip was to Donetsk and Karkov oblasts with Drs. Bebeshko and Dyagil between the 8<sup>th</sup> and 12<sup>th</sup> of September. The trip was preceded by a call from Dr. Romanenko to the Deputy Ministers of the oblasts. The group briefed medical staffs concerning the projects in both trips. They then visited each major hospital and other units concerned with health of the liquidators. There were 12 meetings in 10 visits. They were given a table of organizations. They emphasized the need for the interviews and hematologic studies for which there appeared to be complete agreement. They were advised that Dr. Gudzenko would be coming to work with them for case selection. Dr. Tsvetkova mentioned that Dr. Gudzenko is well known in the registries but not by hematology personnel. The registry personnel and doctors in the oblasts emphasized need for a good microscope, a small amount of reagents, a computer and a centrifuge. They felt that these would be needed for Phase II operations. Dr. Bebeshko is of the opinion that the doctors in these areas were professionally very good. The visits to the oblasts identified other problems. In some of the oblasts the registry for the liquidators is located in special dispensaries (Dnepropetrovsk, Donetsk and Sumskaya) but in others it is part of a general oblast registry. This makes it difficult to give accurate liquidator visits by year because the information is not separated from that of the general population. (In 1 registry there are 22,000 liquidators plus 7,000 evacuees in a population of 2 million people.) From Dnepropetrovsk and Sumskaya the patients often are sent to Kiev for therapy but rarely are they sent to Kiev from Donetsk or Karkov. They usually send their patients to Moscow. It was pointed out that no oblasts

save the peripheral blood smears and their biological materials often are maintained in very poor condition. In Sumskaya bone marrow smears are saved only for 3 years but are saved for much longer periods in the other 4 oblasts. Except for Kiev the FAB system rarely is employed. It was noted that prior to Chernobyl virtually all hematology in Kiev was centered in the Institute of Hematology and Blood Transfusion. Drs. Bebeshko, Dyagil and Klimenko all were located there. Now the clinical work is very fragmented around the city.

Wednesday afternoon I met with Drs. Bazyka and Pilinskaya. Dr. Bazyka pointed out that Dr. Pilinskaya's lamp now is in customs and is only awaiting clearance. He noted that the filter and probes were ordered but that they had not arrived. Dr. Bazyka stated that in the past a batch of culture media had been sent by regular mail and not by FedEx. It had stayed at room temperature for 2 weeks and had spoiled. He also felt that there was some confusion about distribution of culture media. Dr. Bebeshko's RPMI had been ordered through Sigma and had been sent to his laboratory. Dr. Pilinskaya's RPMI had been ordered through Gibco and is as yet not been received. He did not feel that there were any problems in distribution of laboratory reagents. He noted that some of the monoclonal antibodies have come by FedEx and that they were maintained in a refrigerator. He stated that they had not yet receive the M & N antibodies. Dr. Bazyka then gave me a follow-up on Dr. Azarkova who had been scheduled to spend fellowship time in Dr. Blakely's laboratory in AFRRI in Bethesda. This fellowship is to be supported by IAEA. Apparently Dr. Azarkova was advised early last year that she needed more English training before she should accept the fellowship. Since that time she studied and passed the written test in November of 1997 and after 3 months of intensive English training she now has passed the oral examination. The results have been sent to IAEA. All her papers now are in Vienna and it appears that she will be notified in the future when final arrangements have been made for her to initiate her fellowship training period.

Discussions later in the afternoon were held with Dr. Gudzenko. She stated that contact with liquidators at the time of their routine annual visit is quite impractical. She felt a contactor would have to move about to many places in order to meet with these individuals. She believes it is better to make appointments and have trained interviewers in each oblast see the liquidators at scheduled times. Dr. Gudzenko did not realize that blood drawn from the liquidators is to be processed as shown in the algorithm in section 8.3.2 of the protocol. She was pleased that the size of the blood sample to be obtained now has been reduced to 20ml. She also was advised that Dr. Pilinskaya would like the blood sent to her laboratory at room temperature for FISH and Dr. Dyagil would like it on ice for mononuclear cell and plasma separation and storage. Again it was emphasized that since Dr. Pilinskaya is unable to do FISH determinations at this time that the mononuclear cells would be processed only to the pellet stage at this time. Later FISH may be done on some of the pellets. Perhaps the blood from at least 10 of the 20 liquidators for whom blood is removed can be completely processed in accord with the requirements of task #30.

Dr. Burch and I departed from Kiev early in the AM of Thursday (9/24/98).